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L1: Entry 14 of 28 File: USPT May 1, 2001

DOCUMENT-IDENTIFIER: US 6224903 B1
** See image for Certificate of Correction **
TITLE: Polymer-lipid conjugate for fusion of target membranes

Detailed Description Text (8):
As shown in FIG. 1 and in detail in FIG. 2A, hydrophilic polymer chain 16 forms the distal end of a diblock copolymer lipid conjugate 20 having a vesicle-forming lipid moiety 20a and a diblock copolymer moiety 20b. Diblock copolymer moiety 20b, in turn, consists of a hydrophobic chain 22 which is covalently bound at its proximal end to the polar head group of lipid moiety 20a. Hydrophobic chain 22 is bound at its distal end to hydrophilic polymer chain 16 through a chemically releasable bond 24.

Detailed Description Text (28):
As described above, the hydrophilic polymer coating is formed by including, at least in the outer lipid layer of the liposomes, vesicle-forming lipid conjugates containing a diblock copolymer conjugate of the type shown in FIG. 2A, and optionally, hydrophilic polymers directly linked to the head group of a vesicle-forming lipid, as shown in FIG. 3.

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L1: Entry 17 of 28 File: USPT Apr 6, 1999

DOCUMENT-IDENTIFIER: US 5891468 A
TITLE: Fusogenic liposome compositions and method

Detailed Description Text (6):
As shown in FIG. 1 and in detail in FIG. 2A, hydrophilic polymer chain 16 forms the distal end of a diblock copolymer lipid conjugate 20 having a vesicle-forming lipid moiety 20a and a diblock copolymer moiety 20b. Diblock copolymer moiety 20b, in turn, consists of a hydrophobic chain 22 which is covalently bound at its proximal end to the polar head group of lipid moiety 20a. Hydrophobic chain 22 is bound at its distal end to hydrophilic polymer chain 16 through a chemically releasable bond 24.

Detailed Description Text (27):
As described above, the hydrophilic polymer coating is formed by including, at least in the outer lipid layer of the liposomes, vesicle-forming lipid conjugates containing a diblock copolymer conjugate of the type shown in FIG. 2A, and optionally, hydrophilic polymers directly linked to the head group of a vesicle-forming lipid, as shown in FIG. 3.

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WEST Search History

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☐	L7	vesicle same $ethyleneoxide	3
☐	L6	vesicle adj10 $ethyleneoxide	0
☐	L5	vesicle adj5 $ethyleneoxide	0
☐	L4	polymersome	2
☐	L3	polymersome same protein	0
☐	L2	polymersome same enzyme	0
☐	L1	vesicle adj5 ($block)	28

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L8: Entry 12 of 35 File: USPT Nov 5, 2002

DOCUMENT-IDENTIFIER: US 6475517 B1
TITLE: Method for preparing closed vesicles

Detailed Description Text (5):
Also in the specification, the term "closed vesicles" means closed structures consisting of the micelle particles or micelles as mentioned above. Examples include naturally derived closed vesicles such as cells or viruses, and artificial closed vesicles such as liposomes, Novasome (trade name, Micro Vesicular Systems, Inc.) described in Liposome Technology 2nd edition, Vol. 1, p142 (1993), non-ionic surfactant vesicles described in Liposome Technology 2nd edition, Vol. 1, p157 (1993), and polymer microspheres. Among them, liposomes may preferably be used for the present invention.

Detailed Description Text (7):
Examples of the lipids which can constitute the closed vesicles of the present invention include, for example, phospholipids such as naturally derived lecithin (e.g., egg yolk lecithin, soybean lecithin), dipalmitoylphosphatidylcholine (DPPC), dimyristoylphosphatidylcholine (DMPC), distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dimyristoylphosphatidylethanolamine (DMPE), diparmitoylphosphatidylglycerol (DPPG), and dimyristoylphosphatidic acid (DMPA); glycolipids such as glycosphingolipids and glyceroglycolipids; fatty acids; dialkylmethylammonium amphiphiles, polyglycerol alkylethers, polyoxyethylene alkylethers (Liposome Technology 2nd edition, Vol. 1, p.141, 1993); alkyl glycosides; alkyl methylglucamides; alkyl sucrose esters; dialkyl polyoxyethylene ethers; dialkyl polyglycerol ethers (Liposome Technology 2nd edition, Vol. 1, p.157, 1993); and amphipathic block copolymers such as polyoxyethylene/polylactic acids (Japanese Patent Unexamined Publication for PCT applications (KOHYO) No. (Hei) 6-508831/1994). These lipids may be used alone or in combination of two or more of them, and together with one or more non-polar substances such as cholesterol, if desired.

Detailed Description Text (12):
Examples of the diagnostic agents which can be introduced into the closed vesicle include, for example, imaging agents containing radioisotopes such as indium or technetium; contrasting agents containing iodine or gadolinium; enzymes such as horse radish peroxidase, alkaline phosphatase, or .beta.-galactosidase; fluorescent substances such as europium derivatives; luminescent substances such as N-methylacrydium derivatives or the like.

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L8: Entry 17 of 35 File: USPT Oct 2, 2001

DOCUMENT-IDENTIFIER: US 6296870 B1
TITLE: Liposomes containing active agents

Drawing Description Text (49):
In one series of experiments, the present inventors studied the influence of grafted PEG(750) as PEG-lipids on monooleoylphosphatidylcholine (MOPC) monomer exchange and micelle fusion with lipid bilayer vesicle membranes. The experimental results show that PEG(750)-lipid has a strong inhibitory effect such that micelle-membrane fusion decreases with increasing surface density of grafted PEG(750). At approximately 20 mol % PEG-lipid (corresponding to complete coverage of the membrane surface by PEG(750) "mushroom" structures as described below), micelle/membrane fusion is essentially prevented. The experimental data of the present inventors are well described by a model in which micelle-membrane fusion is considered a first order reaction process. The modeling of micelle-membrane fusion in the presence of grafted PEG(750), and the consideration of geometry characteristics of both PEG(750) "mushroom" and MOPC micelle, show that micelles must be in intimate contact with the headgroups of the membrane lipids in order for the fusion process to occur. Thermodynamic analysis and stationary equilibrium Both suggest that the solution properties of surfactant in the aqueous and bilayer phases are not ideal, and that the surfactant molecules are slightly aggregated on average as trimers in the aqueous phase below the CMC. There may also be aggregation of surfactant molecules in the vesicle bilayer when exposed to surfactant concentrations above the CMC and this would be a first indication of defect formation that ultimately results in vesicle membrane breakdown and dissolution of the vesicle.

Drawing Description Text (104):
Gangliosides attached to the membrane surfaces would provide barriers to micelle fusion; for example, short gangliosides containing about four sugar moieties would provide barriers to micelle/membrane fusion. Other molecules of approximately the same size as micelles contained within a liposome could also be utilized to block micelle/membrane binding. Such molecules include, for example, globular proteins such as albumin, and filamentous proteins or peptides. Such molecules could, for example, be attached to the membrane by hydrostatic forces or, if a molecule with an amphipathic "tail" is used, the amphipathic tail could be used to attach the molecule to the membrane. Additionally, one member of a binding pair of molecules could be attached to the liposome membrane so that, when the liposome is exposed to the other member of the binding pair, the conjoined binding pair molecules provide a barrier to membrane/micelle fusion (e.g., a receptor molecule may be attached to the liposome membrane which, by itself, may not inhibit membrane/micelle fusion, but when associated with its ligand the combined receptor-ligand complex is able to inhibit membrane/micelle fusion) . Molecules suitable for use as barriers to membrane/micelle fusion may also act as active agents, including as therapeutic agents.

Drawing Description Text (134):
The derivatized lipid components of liposomes according to the present invention may additionally include a labile lipid-polymer linkage, such as a peptide, ester, or disulfide linkage, which can he cleaved under selective physiological conditions, such as in the presence of peptidase or esterase enzymes or reducing

agents. Use of such linkages to couple polymers to phospholipids allows the attainment of high blood levels of such liposomes for several hours after administration, followed by cleavage of the reversible linkages and removal of the polymer from the exterior liposome bilayer. The polymer-less liposomes are then subject to rapid uptake by the RES system. See, e.g.., U.S. Pat. No. 5,356,633 to Woodle et al).

Drawing Description Text (135):
Additionally, liposomes according to the present invention may contain non-polymer molecules bound to the exterior of the liposome, such as haptens, enzymes, antibodies or antibody fragments, cytokines and hormones (see, e.g., U.S. Pat. No. 5,527,528 to Allen et al), and other small proteins, polypeptides, or non-protein molecules which confer a particular enzymatic or surface recognition feature to the liposome. See published PCT application WO 94/21235. Surface molecules which preferentially target the liposome to specific organs or cell types are referred to herein as "targetting molecules" and include, for example, antibodies which target the liposome to tumor cells bearing specific antigens. Techniques for coupling surface molecules to liposomes are known in the art (see, e.g., U.S. Pat. No. 4,762,915 to Kung et al).

Drawing Description Text (149):
The surprising results obtained by the present inventors show that the inclusion of relatively small amounts of cholesterol in a liposome membrane (amounts too small to create any global stiffening of the membrane) are sufficient to inhibit fusion of micelles with the liposome membrane. It is proposed by the present inventors that the cholesterol perturbs a transition state complex that facilitates micelle/membrane fusion (and ultimately membrane dissolution). These results further indicate that any other molecule that enhances convex curvature (i.e., the normal curvature of a lipid bilayer membrane) and opposes concave curvature (i.e., curvature opposite that found in lipid bilayer membranes) would, like cholesterol, inhibit micelle membrane fusion when the molecule is contained in the lipid bilayer membrane at or above the threshold amount. Suitable molecules would include additional micelle forming surfactants, lipids or polymers, such as short diblock copolymers of polypropylene oxide-polyethylene oxide (PPO-PEO).

Detailed Description Text (94):
The present experiment shows that (1) vesicles can be formed in high concentrations of micelle surfactants; (2) such vesicles are stable until acted on by a disrupting force, and (3) the micelles are encapsulated inside the vesicles.

Detailed Description Text (102):
The results of the above trials showed that (1) vesicles can be formed in high concentrations of micelle surfactants; (2) such vesicles are stable until acted upon by a disrupting force, and (3) micelles are stably encapsulated inside such vesicles.

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L8: Entry 26 of 35 File: USPT Sep 21, 1999

DOCUMENT-IDENTIFIER: US 5954998 A
TITLE: Liquid peracid precursor colloidal dispersions: oil-core vesicles

Detailed Description Text (16):
"Oil-core Vesicles" as used herein pertains to those surfactant bilayer vesicles which contain emulsified oil drops at the interior of the vesicle.

Detailed Description Text (69):
Other nonionic surfactants which may be used include: TAGAT TO (Goldschmidt Chemical Corp.), TWEEN 85 (ICI Surfactants), and EMULPHOR TO-9 (Rhone-Poulenc/GAF). Other surfactants which may be used are block copolymers of propylene oxide and ethylene oxide known under the trade name of PLURONIC.RTM. (BASF Corp.). Anionic surfactants which may be used include, in particular, BIOSOF.RTM. (Stepan). Cationic, amphoteric and zwitterionic surfactants, as well as other nonionic and anionic surfactants which may be used are those described in Kirk-Othmer, Encyclopedia of Chemical Technology, 3rd ed., Volume 22, pp. 332-432 (Marcel-Dekker, 1983), which are incorporated herein by reference. The surfactant comprises about 2% to 40% by weight, more preferably about 2.5% to 30% by weight, and most preferably about 5% to about 25% by weight of the total colloidal dispersion. The surfactant which may be used may be selected from the group consisting of nonionic, amphoteric or zwitterionic surfactants, or a combination thereof, although it is preferred that at least one nonionic surfactant be used.

Detailed Description Text (91):
The colloidal dispersions of the present invention may optionally contain certain adjuncts in addition to the required elements described above. Suitable examples of adjuncts which may be included in the present invention include, without limitation, buffering agents (including alkalinity sources), chelating agents, codispersants, surfactants, enzymes, fluorescent whitening agents (FWA's), electrolytes, builders, antioxidants, thickeners, fragrance, dyes, colorants, pigments, etc., as well as mixtures thereof.

Detailed Description Text (103):
Small amounts of other adjuncts can be added to the various executions of the present invention for improving cleaning performance or aesthetic qualities of the formulated product. Performance adjuncts include surfactants, solvents, enzymes, fluorescent whitening agents (FWA's), electrolytes and builders, anti-foaming agents, foam boosters, preservatives (if necessary), antioxidants and opacifiers, etc. See Gray, et al., U.S. Pat. No. 5,019,289 and U.S. Pat. No. 4,891,147, incorporated by reference herein. When builders or electrolytes are used, they may be incorporated as dispersed particles within the colloidal dispersion in a first portion of a delivery execution. Alternately, builders or electrolytes may also be included in a liquid delivered as part of a second portion of a delivery execution.

Detailed Description Text (120):
In Example 2 below, an alkanoylglycoyl benzene was incorporated into a pre-existing water-core surfactant vesicle system. The peracid precursor NOGB was mixed with a NOVASOME.TM. sample containing 20% surfactant and lipid materials in water. The mixture was stirred at room temperature for 10 minutes and then diluted with

distilled water. The resulting mixture was stirred for another 10 minutes, sonicated for 2 hrs, and then kept at room temperature overnight. Alternately, the NOGB could be preemulsified with a surfactant of choice before being sonicated with the NoVASOME.TM. vesicles. Characterization of the above precursor-surfactant mixture by Fourier-transform infrared spectroscopy (Fr-IR), electron microscopy and differential scanning calorimetry revealed the existence of NOGB-incorporated ellipsoidal unilamellar surfactant vesicles in which most of the NOGB was present in the form of oil droplets encapsulated at the internal core of the closed bilayer structure.

CLAIMS:

6. The stable liquid peracid precursor composition of claim 1 further comprising:

(e) an adjunct selected from the group consisting of buffering agents, chelating agents, codispersants, solvents, enzymes, fluorescent whitening agents (FWA's), electrolytes, antioxidants, builders, anti-foaming agents, foam boosters, preservatives, opacifiers, thickeners, fragrances, dyes, colorants, pigments and mixtures thereof.

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L8: Entry 27 of 35 File: USPT Mar 16, 1999

DOCUMENT-IDENTIFIER: US 5882679 A
TITLE: Liposomes containing active agents aggregated with lipid surfactants

Detailed Description Text (8):
In one series of experiments, the present inventors studied the influence of grafted PEG(750) as PEG-lipids on monooleoylphosphatidylcholine (MOPC) monomer exchange and micelle fusion with lipid bilayer vesicle membranes. The experimental results show that PEG(750)-lipid has a strong inhibitory effect such that micelle-membrane fusion decreases with increasing surface density of grafted PEG(750). At approximately 20 mol % PEG-lipid (corresponding to complete coverage of the membrane surface by PEG(750) "mushroom" structures as described below), micelle/membrane fusion is essentially prevented. The experimental data of the present inventors are well described by a model in which micelle-membrane fusion is considered a first order reaction process. The modeling of micelle-membrane fusion in the presence of grafted PEG(750), and the consideration of geometry characteristics of both PEG(750) "mushroom" and MOPC micelle, show that micelles must be in intimate contact with the headgroups of the membrane lipids in order for the fusion process to occur. Thermodynamic analysis and stationary equilibrium both suggest that the solution properties of surfactant in the aqueous and bilayer phases are not ideal, and that the surfactant molecules are slightly aggregated on average as trimers in the aqueous phase below the CMC. There may also be aggregation of surfactant molecules in the vesicle bilayer when exposed to surfactant concentrations above the CMC and this would be a first indication of defect formation that ultimately results in vesicle membrane breakdown and dissolution of the vesicle.

Detailed Description Text (61):
Gangliosides attached to the membrane surfaces would provide barriers to micelle fusion; for example, short gangliosides containing about four sugar moieties would provide barriers to micelle/membrane fusion. Other molecules of approximately the same size as micelles contained within a liposome could also be utilized to block micelle/membrane binding. Such molecules include, for example, globular proteins such as albumin, and filamentous proteins or peptides. Such molecules could, for example, be attached to the membrane by hydrostatic forces or, if a molecule with an amphipathic "tail" is used, the amphipathic tail could be used to attach the molecule to the membrane. Additionally, one member of a binding pair of molecules could be attached to the liposome membrane so that, when the liposome is exposed to the other member of the binding pair, the conjoined binding pair molecules provide a barrier to membrane/micelle fusion (e.g., a receptor molecule may be attached to the liposome membrane which, by itself, may not inhibit membrane/micelle fusion, but when associated with its ligand the combined receptor-ligand complex is able to inhibit membrane/micelle fusion). Molecules suitable for use as barriers to membrane/micelle fusion may also act as active agents, including as therapeutic agents.

Detailed Description Text (91):
The derivatized lipid components of liposomes according to the present invention may additionally include a labile lipid-polymer linkage, such as a peptide, ester, or disulfide linkage, which can be cleaved under selective physiological conditions, such as in the presence of peptidase or esterase enzymes or reducing

agents. Use of such linkages to couple polymers to phospholipids allows the attainment of high blood levels of such liposomes for several hours after administration, followed by cleavage of the reversible linkages and removal of the polymer from the exterior liposome bilayer. The polymer-less liposomes are then subject to rapid uptake by the RES system. See, e.g., U.S. Pat. No. 5,356,633 to Woodle et al).

Detailed Description Text (92):
Additionally, liposomes according to the present invention may contain non-polymer molecules bound to the exterior of the liposome, such as haptens, enzymes, antibodies or antibody fragments, cytokines and hormones (see, e.g., U.S. Pat. No. 5,527,528 to Allen et al), and other small proteins, polypeptides, or non-protein molecules which confer a particular enzymatic or surface recognition feature to the liposome. See published PCT application WO 94/21235. Surface molecules which preferentially target the liposome to specific organs or cell types are referred to herein as "targetting molecules" and include, for example, antibodies which target the liposome to tumor cells bearing specific antigens. Techniques for coupling surface molecules to liposomes are known in the art (see, e.g., U.S. Pat. No. 4,762,915 to Kung et al).

Detailed Description Text (106):
The surprising results obtained by the present inventors show that the inclusion of relatively small amounts of cholesterol in a liposome membrane (amounts too small to create any global stiffening of the membrane) are sufficient to inhibit fusion of micelles with the liposome membrane. It is proposed by the present inventors that the cholesterol perturbs a transition state complex that facilitates micelle/membrane fusion (and ultimately membrane dissolution). These results further indicate that any other molecule that enhances convex curvature (i.e., the normal curvature of a lipid bilayer membrane) and opposes concave curvature (i.e., curvature opposite that found in lipid bilayer membranes) would, like cholesterol, inhibit micelle membrane fusion when the molecule is contained in the lipid bilayer membrane at or above the threshold amount. Suitable molecules would include additional micelle forming surfactants, lipids or polymers, such as short diblock copolymers of polypropylene oxide-polyethylene oxide (PPO-PEO).

Detailed Description Text (200):
The present experiment shows that (1) vesicles can be formed in high concentrations of micelle surfactants; (2) such vesicles are stable until acted on by a disrupting force, and (3) the micelles are encapsulated inside the vesicles.

Detailed Description Text (208):
The results of the above trials showed that (1) vesicles can be formed in high concentrations of micelle surfactants; (2) such vesicles are stable until acted upon by a disrupting force, and (3) micelles are stably encapsulated inside such vesicles.

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L8: Entry 30 of 35 File: USPT Dec 8, 1998

DOCUMENT-IDENTIFIER: US 5846951 A
** See image for Certificate of Correction **
TITLE: Pharmaceutical compositions

Brief Summary Text (2):
There exists a great variety of pharmacologically active agents for which there is a need either to maintain an elevated concentration in the circulating blood or to deliver them directly to the site of action. Such agents include conventional drugs, peptides and proteins and oligonucleotides used in cancer and antimicrobial therapy and in enzyme or hormone replacement therapy and in immunology. In many instances, agents exhibit a short half-life in the circulation being rapidly excreted through the kidneys or taken up by the reticuloendothelial system (RES) and other tissues. To compensate for such premature drug loss, larger doses are required so that sufficient amounts of drug can concentrate in areas in need of treatment. However this is not only costly, it can also lead to toxicity and an immune response to the "foreign protein". For instance, cytokines such as interferon (IFN-.gamma.) and interleukin-2 (IL-2) would be more effective, less toxic and also used in smaller quantities, if their presence in the circulation could be extended.

Brief Summary Text (6):
Drugs can either be covalently linked to, or passively entrapped into, the DDS. For instance, PDDS comprising surfactant vesicles or liposomes may entrap hydrophilic or hydrophobic pharmaceutically active compounds by being formed of an appropriate combination of layers of surfactant or lipid molecules. Pharmaceutically active compounds are usually covalently linked to MDDS, by a bond which may or may not be lysed in the body, for instance before or after the active compound performs its function. Liposomes are discussed by Gregoriadis in NIPS, 4, 146-151 (1989) and in "Liposomes as Drug Carriers: Recent Trends and Progress" Ed Gregoriadis (1988) Wiley.

Brief Summary Text (10):
Synthetic polymers used in the macromolecular type MDDS are for instance poly (hydroxypropylmethacrylamide) polylysine and polymerised alkyl cyanoacrylates. These may be catabolised in the RES system or other tissues by appropriate lysosomal enzymes. It would be desirable to reduce the rate of catabolism of such biodegradable macromolecular type DDS by some means, for instance by reducing uptake of the DDS by the RES or other tissues, or by reducing degradation by lysosomal enzymes once taken up by the RES.

Brief Summary Text (11):
Particulate DDS (PDDS) are, as a rule, removed from the circulation by the RES. Because of their propensity for the RES, PDDS are often used for the delivery of drugs to these tissues. It is often desirable, however, that PDDS are directed to tissues other than those of the RES. To achieve this goal, one must block or delay RES interception of PDDS.

Brief Summary Text (12):
This has been accomplished to some extent by coating PDDS with hydrophilic macromolecules such as polyethyleneglycol (PEG) or of ethylene oxide and propylene

oxide, including such blocks formed of ethylene diamine, available under the trade names Pluronic, Tetronic, Poloxamer and Poloxamine. These polymers are man made. Their use is described in by Illum in GB-A-2185397, by Illum and Davis in FEBS Letts. (1984) 167, 79-82, by Illum et al in Life Sciences (1987) 40, 367-374, by Hunter et al Scand. J. Immunol. 23, 287 (1986), by Senior et al in Biochem. Biophys. Acta (1991) 1062, 77-82 and in WO-A-9004384. PEG and block copolymers of ethylene oxide are highly hydrophilic, a property which is responsible for their ability to prevent or delay (a) recognition of PDDS (to which such polymers are attached) by tissues which take them up prematurely; (b) loss of drugs, peptides and proteins (to which such polymers are attached) through premature excretion or uptake by irrelevant tissues.

Brief Summary Text (13):
Abuchowski et al in J. Biol. Chem. (1977) 252, 3282-86 disclose the covalent attachment of PEG of two molecular weights (1900 and 5000) to catalase, which reduced the immunogenicity of the protein and increased its half life in the circulation of mice. Abuchowski suggests the process would allow the use of enzyme therapy for instance to alter blood metabolites or to treat storage diseases. However it would be desirable to increase the half life of proteins (and peptides etc) even further than PEG would appear to be capable.

Brief Summary Text (14):
Abuchowski et al also disclose that they rejected the idea of using dextran (a polysaccharide) in place of PEG since dextran is known to be immunogenic in humans. In GB-A-2185397 it is suggested that polysaccharides, xanthan and hyaluronic acid could be used in place of ethylene oxide-propylene oxide block copolymers to prevent uptake by the liver of colloidal particles. The presence of carboxyl groups in xanthan gum is said to be of benefit for the desired effect. No polysaccharides are actually tested nor is any information given as to how polysaccharides might be linked to the colloidal particle surface.

Brief Summary Text (45):
Examples of covalent interactions between the polysaccharide compound and a liposome could be via phosphate ester linkages between the glycerophosphate head groups of the phospholipids. The covalent bonds may be formed either before or after formation of the phospholipids into vesicles. Alternatively, the polysaccharide may be linked to lipid components via interactions between the 1-carboxylic acid group of sialic acid, hydroxyl groups on the polysaccharide or amine groups produced by deacetylation and reactive groups on molecules including hydrophobic chains. For instance the hydrophobic molecules may be lipids, especially phosphatidyl ethanolamine derivatives, to the amine group of which covalent linkages may be formed. Likewise covalent interactions between nonionic synthetic surfactant vesicles and polysaccharide compounds may be via ester, amide or ether linkages onto the hydrophilic portions of the molecules, formed either before or after formation of the vesicles.

Brief Summary Text (46):
Alternatively, the polysaccharide compound may be non-covalently linked to a PDDS component. Non-covalent linkages may for instance be hydrogen bonding interactions between hydrophobic portions of the PDDS component and a polysaccharide compound which comprises a hydrophobic group (eg which is a glycolipid) or which has been covalently linked to a hydrophobic group. Such hydrophobic derivatives of the polysaccharide compound may be formed by reacting the 1-carboxylic acid group of a sialic acid residue in the polysaccharide compound or a hydroxylic group of the polysaccharide compound or an aldehyde derivative of a polysaccharide molecule, for instance with a hydroxyl group, a carboxylic acid group, a halogen atom or an amine group. For instance a glycolipid compound may be incorporated into the shell of a liposome or surfactant vesicle, with its fatty acid hydrophobic chain portions interacting with the hydrophobic portions of the lipids or surfactants. Polysaccharides B, K92, for instance, would be suitable for use in this

application. The glycolipid would conveniently be incorporated with the surfactants or phospholipids whilst the vesicles were being formed or after formation of the vesicles by equilibration of glycolipid with preformed liposomes.

Brief Summary Text (60):
The present invention is of particular value where the pharmaceutically active compound is one which needs to be available in the circulation of a patient for an extended period. It is of particular use for pharmaceutically active ingredients which comprise proteins formed from recombinant DNA technology, which tend to be taken up rapidly by tissues, where their pharmaceutical activity is not exhibited. Pharmaceutically active compounds whose availability in the circulation would be beneficially prolonged by the invention are interleukins, for instance IL-2, IL-6 or IL-1 interferons, tumour necrosis factor (TNF) as well as enzymes for instance for use in enzyme therapy as described by Abuchowski (op. cit.) etc. Another class of compounds which may be beneficially used in the invention are compounds which compete with viruses, for instance HIV, for interaction with certain receptors present on cells in the bloodstream. One type of active compound which may be used in the invention is fluorescent agents which can be used in clinical investigations. For instance fluorescein derivatives may be directly coupled to a polysaccharide compound or may be incorporated into liposomes which are coated with polysaccharide compound. Active ingredients which would usefully be incorporated into liposomes or other DDS include cytostatics, cytokines, antibiotics, haemoglobin, enzymes, hormones, steroids etc.

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L8: Entry 31 of 35 File: USPT Oct 27, 1998

DOCUMENT-IDENTIFIER: US 5827533 A
** See image for Certificate of Correction **
TITLE: Liposomes containing active agents aggregated with lipid surfactants

Detailed Description Text (8):
In one series of experiments, the present inventors studied the influence of grafted PEG(750) as PEG-lipids on monooleoylphosphatidylcholine (MOPC) monomer exchange and micelle fusion with lipid bilayer vesicle membranes. The experimental results show that PEG(750)-lipid has a strong inhibitory effect such that micelle-membrane fusion decreases with increasing surface density of grafted PEG(750). At approximately 20 mol % PEG-lipid (corresponding to complete coverage of the membrane surface by PEG(750) "mushroom" structures as described below), micelle/membrane fusion is essentially prevented. The experimental data of the present inventors are well described by a model in which micelle-membrane fusion is considered a first order reaction process. The modeling of micelle-membrane fusion in the presence of grafted PEG(750), and the consideration of geometry characteristics of both PEG(750) "mushroom" and MOPC micelle, show that micelles must be in intimate contact with the headgroups of the membrane lipids in order for the fusion process to occur. Thermodynamic analysis and stationary equilibrium both suggest that the solution properties of surfactant in the aqueous and bilayer phases are not ideal, and that the surfactant molecules are slightly aggregated on average as trimers in the aqueous phase below the CMC. There may also be aggregation of surfactant molecules in the vesicle bilayer when exposed to surfactant concentrations above the CMC and this would be a first indication of defect formation that ultimately results in vesicle membrane breakdown and dissolution of the vesicle.

Detailed Description Text (60):
Gangliosides attached to the membrane surfaces would provide barriers to micelle fusion; for example, short gangliosides containing about four sugar moieties would provide barriers to micelle/membrane fusion. Other molecules of approximately the same size as micelles contained within a liposome could also be utilized to block micelle/membrane binding. Such molecules include, for example, globular proteins such as albumin, and filamentous proteins or peptides. Such molecules could, for example, be attached to the membrane by hydrostatic forces or, if a molecule with an amphipathic "tail" is used, the amphipathic tail could be used to attach the molecule to the membrane. Additionally, one member of a binding pair of molecules could be attached to the liposome membrane so that, when the liposome is exposed to the other member of the binding pair, the conjoined binding pair molecules provide a barrier to membrane/micelle fusion (e.g., a receptor molecule may be attached to the liposome membrane which, by itself, may not inhibit membrane/micelle fusion, but when associated with its ligand the combined receptor-ligand complex is able to inhibit membrane/micelle fusion). Molecules suitable for use as barriers to membrane/micelle fusion may also act as active agents, including as therapeutic agents.

Detailed Description Text (90):
The derivatized lipid components of liposomes according to the present invention may additionally include a labile lipid-polymer linkage, such as a peptide, ester, or disulfide linkage, which can be cleaved under selective physiological

conditions, such as in the presence of peptidase or esterase enzymes or reducing agents. Use of such linkages to couple polymers to phospholipids allows the attainment of high blood levels of such liposomes for several hours after administration, followed by cleavage of the reversible linkages and removal of the polymer from the exterior liposome bilayer. The polymer-less liposomes are then subject to rapid uptake by the RES system. See, e.g., U.S. Pat. No. 5,356,633 to Woodle et al).

Detailed Description Text (91):
Additionally, liposomes according to the present invention may contain non-polymer molecules bound to the exterior of the liposome, such as haptens, enzymes, antibodies or antibody fragments, cytokines and hormones (see, e.g., U.S. Pat. No. 5,527,528 to Allen et al), and other small proteins, polypeptides, or non-protein molecules which confer a particular enzymatic or surface recognition feature to the liposome. See published PCT application WO 94/21235. Surface molecules which preferentially target the liposome to specific organs or cell types are referred to herein as "targetting molecules" and include, for example, antibodies which target the liposome to tumor cells bearing specific antigens. Techniques for coupling surface molecules to liposomes are known in the art (see, e.g., U.S. Pat. No. 4,762,915 to Kung et al).

Detailed Description Text (105):
The surprising results obtained by the present inventors show that the inclusion of relatively small amounts of cholesterol in a liposome membrane (amounts too small to create any global stiffening of the membrane) are sufficient to inhibit fusion of micelles with the liposome membrane. It is proposed by the present inventors that the cholesterol perturbs a transition state complex that facilitates micelle/membrane fusion (and ultimately membrane dissolution). These results further indicate that any other molecule that enhances convex curvature (i.e., the normal curvature of a lipid bilayer membrane) and opposes concave curvature (i.e., curvature opposite that found in lipid bilayer membranes) would, like cholesterol, inhibit micelle membrane fusion when the molecule is contained in the lipid bilayer membrane at or above the threshold amount. Suitable molecules would include additional micelle forming surfactants, lipids or polymers, such as short diblock copolymers of polypropylene oxide-polyethylene oxide (PPO-PEO).

Detailed Description Text (196):
The present experiment shows that (1) vesicles can be formed in high concentrations of micelle surfactants; (2) such vesicles are stable until acted on by a disrupting force, and (3) the micelles are encapsulated inside the vesicles.

Detailed Description Text (207):
The results of the above trials showed that (1) vesicles can be formed in high concentrations of micelle surfactants; (2) such vesicles are stable until acted upon by a disrupting force, and (3) micelles are stably encapsulated inside such vesicles.

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L8: Entry 33 of 35 File: USPT Jul 7, 1998

DOCUMENT-IDENTIFIER: US 5776877 A
TITLE: Liquid peracid precursor colloidal dispersions: macroemulsions

Detailed Description Text (16):
"Oil-core Vesicles" as used herein pertains to those surfactant bilayer vesicles which contain emulsified oil drops at the interior of the vesicle.

Detailed Description Text (73):
Other nonionic surfactants which may be used include: TAGAT TO (Goldschmidt Chemical Corp.), TWEEN 85 (ICI Surfactants), and EMULPHOR TO-9 (Rhone-Poulenc/GAF). Other surfactants which may be used are block copolymers of propylene oxide and ethylene oxide known under the trade name of PLURONIC.RTM. (BASF Corp.). Anionic surfactants which may be used include, in particular, BIOSOFT.RTM. (Stepan). Cationic, amphoteric and zwitterionic surfactants, as well as other nonionic and anionic surfactants which may be used are those described in Kirk-Othmer, Encyclopedia of Chemical Technology, 3rd ed., Volume 22, pp. 332-432 (Marcel-Dekker, 1983), which are incorporated herein by reference. The surfactant comprises about 2% to 40% by weight, more preferably about 2.5% to 30% by weight, and most preferably about 3% to about 25% by weight of the total colloidal dispersion. The surfactant which may be used may be selected from the group consisting of nonionic, amphoteric or zwitterionic surfactants, or a combination thereof, although it is preferred that at least one nonionic surfactant be used.

Detailed Description Text (95):
The colloidal dispersions of the present invention may optionally contain certain adjuncts in addition to the required elements described above. Suitable examples of adjuncts which may be included in the present invention include, without limitation, buffering agents (including alkalinity sources), chelating agents, codispersants, surfactants, enzymes, fluorescent whitening agents (FWA's), electrolytes, builders, antioxidants, thickeners, fragrance, dyes, colorants, pigments, etc., as well as mixtures thereof.

Detailed Description Text (107):
Small amounts of other adjuncts can be added to the various executions of the present invention for improving cleaning performance or aesthetic qualities of the formulated product. Performance adjuncts include surfactants, solvents, enzymes, fluorescent whitening agents (FWA's), electrolytes and builders, anti-foaming agents, foam boosters, preservatives (if necessary), antioxidants and opacifiers, etc. See Gray, et al., U.S. Pat. No. 5,019,289 and U.S. Pat. No. 4,891,147, incorporated by reference herein. When builders or electrolytes are used, they may be incorporated as dispersed particles within the colloidal dispersion in a first portion of a delivery execution. Alternately, builders or electrolytes may also be included in a liquid delivered as part of a second portion of a delivery execution.

L8: Entry 35 of 35 File: USPT Jun 28, 1994

DOCUMENT-IDENTIFIER: US 5324436 A

**** See image for Certificate of Correction ****

TITLE: Use of hydrate formation to control membrane mimetic systems

Drawing Description Text (6):
FIG. 4 illustrates lipase activity maintenance through acyl-enzyme coupling;

Drawing Description Text (8):
FIG. 6 illustrates .alpha.-chymotrypsin activity modifications through hydrate formation where k.sub.app is the apparent rate constant, V.sub.init, the initial rate and E.sub.t, the total enzyme concentration;

Drawing Description Text (9):
FIG. 7 illustrates alternate methods of changing w.sub.o and effects on lipase activity, in which the notation 25e, for example, indicates enzyme containing micelles of w.sub.O =25;

Drawing Description Text (12):
FIG. 10 illustrates enzyme activity inhibition through increased surfactant concentrations (at constant w.sub.o);

Detailed Description Text (5):
Vesicles constructed of relatively simple surfactants are membrane-like structures formed as hydrocarbon bilayers or other molecules and are considered to be spherical bags with diameters of about a few hundred angstroms (A) and a thickness of about 50 A and are osmotically active. Typically, each surfactant vesicle contains 80,000 to 100,000 surfactant molecules.

Detailed Description Text (7):
Generally, vesicles are more stable than micelles to dilution and tend not to break down. Thus, temperature induced phase transition and phase separation offer a means for permeability control and molecular recognition to thereby mimic biological membranes. More specific to this invention is that dilution or the addition of electrolytes can change the size of the model membranes. Hence, the addition of electrolyte shrinks the surfactant vesicles and placing them in solutions that are more dilute than their internal electrolyte concentrations swells the vesicles.

Detailed Description Text (28):
A significant purpose for using the hydrate process is the competition between aggregation and correct refolding. Should aggregation persist, an alternative scheme may be used employing hydrates but encapsulating the protein in reversed micelies. Pressurization of a light hydrocarbon in the presence of bis(2-ethylhexyl) sodium sulfosuccinate (AEROSOL TO, hereafter AOT) and water, leads to solubilization and formation of reversed micelles in the dense gas phase at critical solvent density. See Nguyen, H. et al., "Clathrate Hydrate Formation in Reversed Micellular Solutions," J. Phys. Chem., 93, 8123-8126 (1989); Rao, A. M. et al., "Modification of Enzyme Activity in Reversed Micelles Through Clathrate Hydrate Formation," Biotechnol. Prog., 6, 465-471 (1990); Nguyen, H. et al.,

"Characteristics of Protein-Containing Reversed Micelles Subjected to Clathrate Hydrate Formation Conditions, J. Phys. Chem., 95, 1467-1471 (1991); Phillips, J. B. et al., "Protein Recovery from Reversed Micellar Solutions Through Contact with a Pressurized Gas Phase," Biotechnol. Prog., 7, 43-48 (1991). The relevant disclosures of all references cited herein are incorporated by reference.

Detailed Description Text (50):
Nonionic surfactants may be used in inverse emulsion polymerization. The emulsifiers for polymerization comes in the form of blends, where the most desirable ratio for hydrophile-lipophile is experimentally predictable. For example, a blend of sesquioleate sorbitan and polyoxyethylene sorbitol hexaoleate is desirable for the microemulsification of an aqueous solution of acrylamide or acrylamide-sodium acrylate in an isoparaffinic oil. Further, polymerization of acrylamide has been performed in water-toluene systems stabilized by amphiphilic block copolymers in the presence of 2-propanol.

Detailed Description Text (60):
By practicing the present invention, phenolic and aromatic amine containing polymers have been synthesized with the functional groups on the polymer aligned leading to an oriented polymer having unique properties. Orientation on the polymer is imposed by orienting the individual monomeric units prior to synthesis. The monomers have surfactant properties (i.e., they are amphiphilic). This suggests that in reversed micellar systems they would be oriented at the oil-water interface of the microdroplets with the functional groups (hydroxyl and/or amine) inside the water pools. The micelle contains the catalytic enzyme, such as peroxidase, tyrosinase, laccase or the like, which is then used to close the monomer on the interface.

Detailed Description Text (61):
The present membrane mimetic system can be used to not only synthesize polymers efficiently by enzyme-based polymerization reaction in reversed micellar solution, but to also control the size and morphology of the polymer particles formed. By appropriately adjusting the composition of the reaction medium and by controlling the amount of any added reaction mediating compound, such as hydrogen peroxide, supplied externally or generated in situ, the size of the finely dispersed polymer particles formed can be adjusted. In particular, spherical particles of micron and submicron size can be formed when the polymerization reaction is effected in reversed micelles containing a liquid hydrocarbon solvent and a surfactant. The polymers thus enzymatically synthesized at a surfactant concentration of from at least 0.01M have definite morphologies as opposed to those of comparable polymers synthesized in monophasic organic solvents.

Detailed Description Text (62):
In one preferred polymer synthesis embodiment, the enzyme concentration can range upwards from a minimum of about 0.1 mg/ml; and the substrate (monomer) concentration can range from a monomer to surfactant ratio of about 0.1 to about 10 upwards to a monomer to surfactant ratio of about 10 to about 1. A preferred reaction mediating compound is a source of hydrogen peroxide but is not limited thereto. Preferably liquid hydrogen peroxide is added to provide a molar concentration in excess of the monomer concentration. Alternatively, the reaction mediating compound can be generated in situ. For example, glucose oxidase can be encapsulated along with peroxidase, in the reversed micelles and glucose added to generate hydrogen peroxide in situ. To date it has also been found that the catalytic enzyme, tyrosinase, does not require added hydrogen peroxide to catalyze the polymerization.

Detailed Description Text (71):
Another environmental application of this invention is the removal of phenolic and aromatic amine contaminants from aqueous streams by polymerizing them to insoluble polymers and thus precipitating them from aqueous solution. Surfactants can be

added to concentrate the contaminants from the aqueous streams and the contaminants are then encapsulated into micelies. The enzymes can then polymerize the micelles and take the polymers containing the contaminants out of the solution. The contaminants can then be isolated since the surfactants biodegrade and are much shorter lived than the contaminants.

Detailed Description Text (76):
This example illustrates two membrane mimetic systems prepared from enzyme-encapsulated reversed micellar solutions of lipase and .alpha.-chymotrypsin and gas hydrates.

Detailed Description Text (77):
The enzymes, lipase from Candida cylindracea, and .alpha.-chymotrypsin, the substrates oleic acid and N-glutaryl-L-phenylalanine-p-nitroanilide (GPNA) were obtained from Sigma Chemical Co.; and octanol was obtained from Aldrich Chemical Co. Reversed micelle constituents included the anionic surfactant bis(2-ethylhexyl) sulfosuccinate sodium salt (AOT) and isooctane (99% purity), both obtained from Aldrich. Methane (>99.9% purity, Matheson) was used as the hydrate-forming gas. Double-distilled water was used in buffer preparations.

Detailed Description Text (78):
Enzyme-encapsulated reversed micellar solutions were prepared by the injection method generally as follows. Each individual enzyme was first separately dissolved in aqueous buffer at its appropriate respective pH; namely, pH 7.5 for lipase in 0.01 M phosphate buffer and pH 10.5 for .alpha.-chymotrypsin in 0.1M glycine/NaOH buffer. Each enzyme-containing aqueous phase was then individually and separately contacted with isooctane containing AOT dissolved therein at the given concentration discussed below. Each mixture was stirred with a magnetic stirrer until an optically transparent reversed micellar solution was obtained.

Detailed Description Text (81):
A 1:1 molar ratio of oleic acid and alcohol was used in all examples; thus the alcohol conversion was directly related to the acid conversion and the ester yield. For .alpha.-chymotrypsin, the procedure followed was described specifically by Barbaric et al., in J. Am. Chem. Soc., 103:4239-4244 (1981) and generally by Luisi, P. L. in Reverse Micelies, published by Plenum N.Y. (1984). This procedure involved introducing into the sample cell of a UV spectrophotometer 0.3 ml of enzyme-containing reversed micelles of a given w.sub.o and 1.2 ml of substrate (GPNA) containing micelles of the same w.sub.o, to give 1.5 ml of solution with final substrate and enzyme concentrations of 0.2 mM and 1.3 .mu.M, respectively.

Detailed Description Text (82):
The same procedure was followed for the reference cell with the exception that the 0.3 ml of reversed micellar solution did not contain any enzyme. The difference between the two cells was only the enzyme content. The reaction was followed by monitoring the absorbance at 366 nm due to the nitroaniline released during the process. See also Luisi, "Enzymes Hosted in Reverse Micelles in Hydrocarbon Solution" Angew. Chem , Int Ed Engl , 24, 439-450 (1985), incorporated herein by reference. The slope of the absorbance vs time plot, linear over the first 15 minutes, was used to determine initial results.

Detailed Description Text (88):
In order to form hydrates at a reasonable pressure, the system was cooled to temperatures approaching about 273 degrees K. For example, hydrate dissociation pressure when methane was used as the hydrate forming gas at about 273.15 degrees K., was 2.76 MPa for reversed micelles with a w.sub.o of about 15; 3.10 MPa for micelles with a w.sub.o of about 10; and 4.83 MPa for micelles with a w.sub.o of about 5. There is thus the need to maintain enzyme activity at low temperatures. Additionally, sampling was done carefully to avoid deactivating the enzyme through shearing during the process.

Detailed Description Text (89):
The process of pressurizing a sampling to 0.1-0.3 MPa below the temperature-controlled hydrate cell and recovering the supernatant across this small pressure gradient results in a sample with little enzyme deactivation. Once the sample was recovered, the pressure in the sampling cell was slowly reduced to atmospheric pressure substantially without destroying enzyme activity. Considerably lower pressures can be used with other gases; for example, xenon forms hydrates in reversed micelles of a w.sub.o of about 15 at about 0.19 MPa and about 273.15K.; the corresponding dissociation pressure for ethylene hydrates is 0.62 MPa. The following hydrates were prepared with methane as the hydrate forming gas species, but is not limited thereto. Protein solubility was completely retained during methane hydrate formation at the chosen temperature (about 273.15K.) and pressures (up to about 6 MPa).

Detailed Description Text (90):
Lipase-catalyzed ester synthesis is a bimolecular reaction involving the substrates oleic acid and octanol. Since both substrates are amphiphilic, reaction proceeds at the interface of the micelle. It was found that the enzyme rapidly loses its activity in reversed micelles unless it is contacted with the acyl substrate, oleic acid as illustrated in FIG. 4. The fresh reaction mixture (filled circles in FIG. 4) denotes the case where the reaction was started by adding both substrates immediately following encapsulation of the enzyme. Incubating the encapsulated enzyme at about 313K. for 24 hours prior to staring the reaction by adding the substrates results in a significantly less active enzyme; the loss of activity was somewhat mitigated by incubation at about 273 K. On the other hand, incubation with the acyl substrate for 24 hours prior to reaction initiation by adding the alcohol results in activity maintenance. Furthermore, the activity was well maintained when incubation with the acyl substrate is carried out at about 273K. rather than at about 313 K. Indeed, a 2-day incubation run at about 273K. also showed good maintenance of activity.

Detailed Description Text (91):
The use of the acyl substrate in stabilizing the enzyme appears reasonable when one considers that the mechanism for lipase catalysis involves initial binding to the acyl substrate as set forth generally by Deleuze et al., in Biochim. Biophys. Acta, 911, 117-120 (1987): ##STR1## where AcX and AcY re the acyl donors (the acid and ester, respectively), AcE is the acyl-enzyme complex, and X and Y are the nucleophilic acyl acceptors (water and alcohol, respectively). Thus, the acyl-enzyme binding may optimally position the enzyme at the interface allowing activity maintenance.

Detailed Description Text (92):
The acyl-enzyme coupling was important in experiments involving hydrates, since the process of hydrate formation and sampling at progressively higher pressures took place over the course of a day or two. Accordingly, the initial sample introduced to the hydrate cell was a lipase-containing reversed micellar solution of w.sub.o about 24 and oleic acid content 0.05M. The presence of the amphiphilic substrate then changed the nature of the micelle, and the pressure v. temperature v. w.sub.o diagram generated for single-surfactant micelles was no longer applicable for the added cosurfactant case. That is, it was not possible to determine simply from the pressure (at a given temperature) what the w.sub.o of the micellar supernatant was, unless a new pressure v. temperature v. w.sub.o diagram was generated for the dual surfactant case. Once the samples were removed from the hydrate cell, they were contacted with 0.05M octanol to initiate reaction, which was carried out in a shake flask maintained at about 313 K.

Detailed Description Text (93):
FIG. 5 illustrates the lipase activity obtained from reversed micelle samples recovered from the hydrate cell at different w.sub.o values over a pressure range

of 2.7-7 MPa at about 273.7K., starting with an initial solution of a w.sub.o about 24. The activities were compared to those obtained from lipase-containing micellar solutions, individually prepared at different w.sub.o values. The maximum activity for the hydrate-modified case was very slightly lower than that for the individual preparation case, and the optimal w.sub.o appeared to be shifted to a lower value. The fact that lipases in reversed micelles exhibited a significant enhancement of activity when the w.sub.o was modified by hydrate formation was indicative of the fact that hydrate formation in the micelles did not lead to enzyme deactivation. The apparent shift in optimal w.sub.o appeared to be the result of changes in the microaqueous environment brought about when apart of the micellar water was removed through hydrate formation.

Detailed Description Text (94):
With .alpha.-chymotrypsin, the reaction was quite different. Although the hydrolysis of GPNA was also bimolecular, one of the substrates (water) was a constituent of the micelies. At the GNPA concentrations used (0.2 mM), less than 0.1% of the micellar water was required for full conversion. The large excess of micellar water implied that there was no effect of the reaction on the w.sub.o of the solution. The hydrate formation test was simply carried out by introducing an enzyme-containing reversed micellar solution at a w.sub.o of about 17, forming hydrates at progressively higher pressures and sampling the supernatant at different pressures. The pressure v. temperature v. w.sub.o data developed for empty micelles held well for this system, and the w.sub.o of the supernatant was determined simply by noting the equilibrated pressure, which was also verified by Karl-Fischer titration. As soon as a supernatant sample was taken from the hydrate cell and its w.sub.o measured, the enzyme activity was assayed.

Detailed Description Text (95):
FIG. 6 is similar to FIG. 5 and illustrates the .alpha.-chymotrypsin activities in micelles of different w.sub.o values, where w.sub.o was adjusted either through individual sample preparation or through hydrate formation. Again, the hydrate formation technique of adjusting w.sub.o led to enzyme activity modifications; the comparable activity in both cases implied that hydrate formation within the micelles did not adversely affect enzyme activity. The small shift to a lower optimal w.sub.o was observed, which was attributed to changes in the microaqueous phase. The optimal w.sub.o for .alpha.-chymotrypsin can be a function of the pH of the buffer from which the micellar solution was prepared. The acidity of the modified microaqueous phase can be examined by using the method of 31.sup.P NMR analysis. See generally Smith et al., "Micellar Solubilization of Biopolymers in Hydrocarbon Solvents. III. Empirical Definition of an Acidity Scale in Reverse Micelies," Helv. Chim. Acta, 63:2302-2311 (1980).

Detailed Description Text (96):
Hydrate formation in enzyme-containing reversed micelles leads to a change in micelle size and a concomitant modification of enzyme activity. Three cases (Case I, II and III) involving other methods of changing w.sub.o and the effect on enzyme activity are illustrated in FIG. 7 for lipase and in FIG. 8 for .alpha.-chymotrypsin.

Detailed Description Text (97):
In Case I empty reversed micelles of much smaller w.sub.o (small micelies) were added to enzyme-containing micelles of higher w.sub.o to yield a micellar solution of the optimal w.sub.o. For example, mixing micellar solutions of a w.sub.o of about 5 and a w.sub.o of about 25 in the volume ratio 3/1 leads to a solution with a w.sub.o of about 10 (FIG. 7). When the enzyme was originally contained in micelles of a w.sub.o of about 25, the procedure resulted in a 3-fold reduction of the enzyme concentration and hence a reduction in total reaction rate. For comparisons of the different cases, the enzyme concentration was adjusted in making up the solutions of a high w.sub.o, so that the final enzyme concentrations were the same in all cases. The notation 25e+5 denotes the mixing of micelles of a

w.sub.o of about 25 (containing enzyme) with micelles of a w.sub.o of about 5. Thus, the notation 25e+5 was identical with 10e in terms of final enzyme:surfactant:water ratios; the only difference being the method of preparation.

Detailed Description Text (98):
In Case II, AOT (in solid form) was added to enzyme-containing reversed micelles of large w.sub.o to bring down the w.sub.o to the optimum value. Here the AOT (and water) concentrations of the final mixture were higher than in Case I. Case II was used to indirectly examine AOT concentration effects on activity. The notation 25e+A in FIG. 7, for example, was applied to Case II.

Detailed Description Text (99):
Case III was a variant of Cases I and II. AOT was dissolved in isooctane (i.e., micelles of a w.sub.o =0), and the dissolved AOT was then added to enzyme-containing micelles of a large w.sub.o. As in Case I, when the AOT concentration was constant, the enzyme concentration decreased upon mixing the two solutions. Hence, as in Case I, the concentration of the enzyme in the solution of a w.sub.o of about 25 was such that the final concentration at a w.sub.o of about 10 was 0.1 mg/ml. The notation for this case in FIG. 7 was 25E+A/I.

Detailed Description Text (101):
Turning to FIGS. 7 and 8, the final enzyme and substrate concentrations were substantially identical in all cases. The AOT concentration for Case II was higher than the other cases, as shown. It was observed that all methods of w.sub.o reduction to a more optimal level resulted in enhanced activity. To some extent, this reflects the fact that reversed micelles are dynamic entities. During the process of collision, constituent exchange, and reformation of micelies, the encapsulated enzyme was perhaps able to alter conformation to a state dictated by the micelle size. However, enzyme activity was not enhanced to the levels obtained by encapsulating enzyme at the appropriate w.sub.o (10e in FIG. 7 and 9e in FIG. 8), indicating that simultaneous encapsulation and reversed micelle formation results in the most active confirmation.

Detailed Description Text (102):
As shown in FIGS. 7 and 8, with increased surfactant concentrations (Case II in FIGS. 9 and 10), the enzyme activity was least enhanced. The inhibitory effect of the surfactant concentration was clearly shown in FIG. 8, where the w.sub.o was maintained constant.

Detailed Description Text (104):
This example illustrates the use of the membrane mimetic system as an organized medium for synthesizing enzyme-catalyzed polymers in reversed micellar solution using p-ethylphenol monomer as the polymerizable substrate, peroxidase as the catalytic enzyme and a peroxide as the reaction mediating compound.

Detailed Description Text (105):
An enzyme-encapsulated reversed micellar solution was first prepared by the injection method as described in Example I, except that the enzyme was horseradish peroxidase (40,000 molecular weight) obtained from Sigma Chemical Co. The peroxidase was dissolved in the buffer, N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid), hereafter HEPES. A stock solution of 1.25 mM peroxidase in HEPES buffer, at a pH of about 7.5, was prepared and about 0.15 Moles AOT was dissolved in isooctane.

Detailed Description Text (106):
Sufficient enzyme-containing aqueous phase was added to the isooctane-AOT solution to achieve an overall enzyme concentration of about 0.5 mg/ml and a buffer concentration of about 1.5M in the reaction mixture. This resulted in a reversed micellar solution having a w.sub.o (buffer to AOT molar ratio) of about 10. A molar

concentration of about 0.15M p-ethylphenol was then added to the reversed micellar solution and dissolved therein. The polymerization reaction was then initiated by adding hydrogen peroxide (30% in water) to provide a molar peroxide concentration of about 0.2M, which is in excess of the monomer concentration. The liquid hydrogen peroxide was added gradually at a controlled rate sufficient to maintain the reaction and avoid deactivating the enzyme.

Detailed Description Text (107):
In another test, hydrogen peroxide as the mediating compound also was generated in situ by a glucose oxidation coupled reaction. In this case, the enzyme glucose oxidase was encapsulated in addition to peroxidase in the reversed micelies. Glucose was then added to produce gluconic acid and hydrogen peroxide. The hydrogen peroxide generated was then used for the polymerization.

Detailed Description Text (108):
The basic reaction mechanism of the addition of a peroxide in the presence of an enzyme forms a transition intermediate state in which the reaction takes place on both positions of the benzyl ring which are ortho to the oxygen substituent of the p-ethylphenol monomer.

Detailed Description Text (110):
FIG. 12 is an electron micrograph taken at 4000.times. magnification of a dried powder of polymer particles of this invention. Reversed micelles were formed from a composition containing about 0.3M AOT, about 0.15M p-ethylphenol buffered to a surfactant molar ratio of about 15:1 with about a 5mg/ml enzyme concentration. Hydrogen peroxide was gradually added in several batches to provide a final concentration of about 0.195M. The polymer particles which formed precipitated out of the solution. The polymer particles were collected by centrifuging and/or filtration. The surfactants were then removed from the polymer by repeated washing with isooctane. The collected particles were then dried to a powder at about 60.degree. C. The electron micrograph of the powder seen in FIG. 12 illustrates the spherical characteristics of the polymer particles.

Detailed Description Text (111):
Similar results were obtained when the procedure was varied by adding enzyme-free HEPES buffer to the isooctane-AOT solution to a buffer concentration of about 1.69M in the solution and then adding an aliquot of the stock enzyme-containing buffer solution to provide an additional buffer concentration of 0.56M for a total buffer 25 concentration of about 2.25M. This procedure produced a reversed micellar solution having a w.sub.o (water to AOT molar ratio) of about 15 and a total enzyme concentration of about 12.5.mu.M.

Detailed Description Text (113):
In one case, the weight percent of the three components was about 25 weight percent buffer, about 25 weight percent surfactant and about 50 weight percent isooctane. In another case, the components were about 3 weight percent surfactant, about 30 weight percent buffer and about 67 weight percent isooctane. The enzyme concentration used in these tests ranged upwards from a minimum of 0.1 mg/ml. The substrate (monomer) concentration varied from a monomer:surfactant concentration of from about 0.1:10 to about 10:1.

Detailed Description Text (118):
While enzymatic polymer synthesis has been illustrated using reversed micelles (water-in-oil microemulsions), it is not limited thereto. Preliminary results using oil-in-water microemulsions for long-chain enzyme-catalyzed polymerization reactions have resulted in enhanced solubility of the growing chain when solvent, such as isooctane, and surfactant are used to prepare the oil-in-water microemulsion.

Other Reference Publication (5):

Kabanov et al., "Enzymes Entrapped in Reversed Micelles of Surfactants in Organic Solvents: A Theoretical Treatment of the Catalytic Activity Regulation", J. Theor. Biol., vol. 133 pp. 327-343 (1988).

Other Reference Publication (7):
Luisi, P. L., "Enzymes Hosted in Reverse Micelles in Hydrocarbon Solution," Angewandte Chemie International Edition in English, vol. 24, pp. 439-450 (1985).

Other Reference Publication (11):
Rao et al., "Modification of Enzyme Activity in Reversed Micelles through Clathrate Hydrate Formation," Biotechnology Progress, vol. 6, pp. 465-471 (1990).

CLAIMS:

9. The method of claim 1 wherein the internal reaction medium comprises an enzyme, at least one polymerizable monomer and water.

11. A method for controlling enzymatic polymer synthesis within the internal reaction medium of a membrane mimetic system, the method comprising the steps of:

a) admixing a first solution comprising at least one enzyme dissolved in aqueous buffer solution with a second solution comprising at least one surfactant dissolved in a liquid hydrocarbon solvent to form a reversed micellar solution;

b) dissolving at least one substrate capable of being polymerized in the reversed micellar solution to provide an internal reaction medium comprising the foregoing solutes; and

c) reversibly isolating a portion of the solvent within the reaction medium so as to raise the effective concentration of the solute in the admixture to a level sufficient to cause a change in the concentration of the solute in the reaction medium.

12. The method of claim 11 wherein the at least one enzyme is a catalytic enzyme selected from the group consisting of peroxidase, tyrosinase and laccase.

18. The method of claim 11 wherein the enzyme is present at a concentration of at least about 0.1 mg/ml.

24. The method of claim 23 wherein the at least one enzyme is peroxidase and the reaction mediating compound is a source of hydrogen peroxide.

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☐ 31. Document ID: US 5827533 A

Using default format because multiple data bases are involved.

L8: Entry 31 of 35 File: USPT Oct 27, 1998

US-PAT-NO: 5827533
DOCUMENT-IDENTIFIER: US 5827533 A
**** See image for Certificate of Correction ****

TITLE: Liposomes containing active agents aggregated with lipid surfactants

DATE-ISSUED: October 27, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Needham; David	Durham	NC		

US-CL-CURRENT: 424/450; 424/1.21, 424/9.32, 424/9.51

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 32. Document ID: US 5792385 A

L8: Entry 32 of 35 File: USPT Aug 11, 1998

US-PAT-NO: 5792385
DOCUMENT-IDENTIFIER: US 5792385 A

TITLE: Liquid peracid precursor colloidal dispersions: liquid crystals

DATE-ISSUED: August 11, 1998

INVENTOR-INFORMATION:

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US-CL-CURRENT: 252/299.01; 510/277

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 33. Document ID: US 5776877 A

L8: Entry 33 of 35 File: USPT Jul 7, 1998

US-PAT-NO: 5776877
DOCUMENT-IDENTIFIER: US 5776877 A

TITLE: Liquid peracid precursor colloidal dispersions: macroemulsions

DATE-ISSUED: July 7, 1998

INVENTOR-INFORMATION:

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Zhou; Boli	Antioch	CA		

US-CL-CURRENT: 510/277; 252/186.38, 252/186.41, 510/303, 510/312

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 34. Document ID: US 5681805 A

L8: Entry 34 of 35 File: USPT Oct 28, 1997

US-PAT-NO: 5681805
DOCUMENT-IDENTIFIER: US 5681805 A

TITLE: Liquid peracid precursor colloidal dispersions: microemulsions

DATE-ISSUED: October 28, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Scheuing; David R.	Danville	CA		
McManus; James D.	Tracy	CA		
Van Buskirk; Gregory	Danville	CA		

US-CL-CURRENT: 510/277; 252/186.38, 252/186.41, 510/312, 510/370, 510/376

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 35. Document ID: US 5324436 A

L8: Entry 35 of 35 File: USPT Jun 28, 1994

US-PAT-NO: 5324436
DOCUMENT-IDENTIFIER: US 5324436 A
**** See image for Certificate of Correction ****

TITLE: Use of hydrate formation to control membrane mimetic systems

DATE-ISSUED: June 28, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
John; Vijay T.	Kenner	LA		
Akkara; Joseph A.	Holliston	MA		
Kaplan; David L.	Stow	MA		

US-CL-CURRENT: 210/638; 210/643

Terms	Documents
L7 and enzyme	35

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Search Results - Record(s) 1 through 30 of 35 returned.

☐ 1. Document ID: US 6800273 B2

Using default format because multiple data bases are involved.

L8: Entry 1 of 35 File: USPT Oct 5, 2004

US-PAT-NO: 6800273
DOCUMENT-IDENTIFIER: US 6800273 B2

TITLE: Pharmaceuticals for the imaging of angiogenic disorders

DATE-ISSUED: October 5, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rajopadhye; Milind	Westford	MA		
Edwards; D. Scott	Burlington	MA		
Barrett; John A.	Groton	MA		
Carpenter, Jr.; Alan P.	Carlisle	MA		
Harris; Thomas D.	Samel	NH		
Heminway; Stuart J.	Lowell	MA		
Liu; Shuang	Chelmsford	MA		
Singh; Prahlad R.	Arlington	MA		

US-CL-CURRENT: 424/1.69; 206/223, 206/569, 206/570, 424/1.11, 424/1.65, 514/2, 534/14

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 2. Document ID: US 6716412 B2

L8: Entry 2 of 35 File: USPT Apr 6, 2004

US-PAT-NO: 6716412
DOCUMENT-IDENTIFIER: US 6716412 B2

TITLE: Methods of ultrasound treatment using gas or gaseous precursor-filled compositions

DATE-ISSUED: April 6, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY

Unger; Evan C. Tucson AZ

US-CL-CURRENT: 424/9.52; 424/450, 424/9.5, 424/9.51, 514/44, 600/437, 604/21

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 3. Document ID: US 6699846 B2

L8: Entry 3 of 35 File: USPT Mar 2, 2004

US-PAT-NO: 6699846
DOCUMENT-IDENTIFIER: US 6699846 B2

TITLE: Mono- and disaccharides for the treatment of nitric oxide related disorders

DATE-ISSUED: March 2, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Elliott; Gary T.	Stevensville	MT		
Johnson; David	Hamilton	MT		
Weber; Patricia	Stevensville	MT		
Sowell; Greg	Bothell	WA		

US-CL-CURRENT: 514/53; 514/175, 514/54, 536/123.13, 536/53, 536/55, 536/55.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 4. Document ID: US 6673908 B1

L8: Entry 4 of 35 File: USPT Jan 6, 2004

US-PAT-NO: 6673908
DOCUMENT-IDENTIFIER: US 6673908 B1

TITLE: Tumor necrosis factor receptor 2

DATE-ISSUED: January 6, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Stanton, Jr.; Vincent P.	Belmont	MA		

US-CL-CURRENT: 536/22.1; 435/6, 435/91.1, 435/91.2, 536/23.1, 536/24.3, 536/24.31, 536/24.33

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 5. Document ID: US 6660498 B1

L8: Entry 5 of 35 File: USPT Dec 9, 2003

US-PAT-NO: 6660498
DOCUMENT-IDENTIFIER: US 6660498 B1

TITLE: Malaria immunogenic composition

DATE-ISSUED: December 9, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hui; George S. N.	Honolulu	HI		
Pang; Lap-Yin	Kwai Chung			HK
Ho; Walter K. K.	Taipo			HK

US-CL-CURRENT: 435/69.1; 435/69.3, 530/412, 530/413, 530/414, 530/415, 530/416, 530/417

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 6. Document ID: US 6635676 B2

L8: Entry 6 of 35 File: USPT Oct 21, 2003

US-PAT-NO: 6635676
DOCUMENT-IDENTIFIER: US 6635676 B2

TITLE: Non-toxic antimicrobial compositions and methods of use

DATE-ISSUED: October 21, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Baker, Jr.; James R.	Ann Arbor	MI		
Hamouda; Tarek	Milan	MI		
Shih; Amy	Ann Arbor	MI		
Myc; Andrzej	Ann Arbor	MI		

US-CL-CURRENT: 514/642; 514/937, 514/938

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 7. Document ID: US 6559189 B2

L8: Entry 7 of 35 File: USPT May 6, 2003

US-PAT-NO: 6559189
DOCUMENT-IDENTIFIER: US 6559189 B2

TITLE: Non-toxic antimicrobial compositions and methods of use

DATE-ISSUED: May 6, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Baker, Jr.; James R.	Ann Arbor	MI		
Hamouda; Tarek	Ypsilanti	MI		
Shih; Amy	Ann Arbor	MI		
Myc; Andrzej	Ann Arbor	MI		

US-CL-CURRENT: 514/642; 424/400, 424/757, 514/537

☐ 8. Document ID: US 6548047 B1

L8: Entry 8 of 35 File: USPT Apr 15, 2003

US-PAT-NO: 6548047
DOCUMENT-IDENTIFIER: US 6548047 B1

TITLE: Thermal preactivation of gaseous precursor filled compositions

DATE-ISSUED: April 15, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		

US-CL-CURRENT: 424/9.51; 424/450, 424/9.4, 424/9.5, 424/9.52

☐ 9. Document ID: US 6537520 B1

L8: Entry 9 of 35 File: USPT Mar 25, 2003

US-PAT-NO: 6537520
DOCUMENT-IDENTIFIER: US 6537520 B1

TITLE: Pharmaceuticals for the imaging of angiogenic disorders

DATE-ISSUED: March 25, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rajopadhye; Milind	Westford	MA		
Edwards; D. Scott	Burlington	MA		
Barrett; John A.	Groton	MA		

Carpenter, Jr.; Alan P.	Carlisle	MA
Harris; Thomas D.	Samel	NH
Heminway; Stuart J.	Lowell	MA
Liu; Shuang	Chelmsford	MA
Singh; Prahlad R.	Arlington	MA

US-CL-CURRENT: 424/1.69; 424/1.11, 424/1.65, 424/9.1, 534/14

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 10. Document ID: US 6506803 B1

L8: Entry 10 of 35 File: USPT Jan 14, 2003

US-PAT-NO: 6506803
DOCUMENT-IDENTIFIER: US 6506803 B1

TITLE: Methods of preventing and treating microbial infections

DATE-ISSUED: January 14, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Baker, Jr.; James R.	Ann Arbor	MI		
Hamouda; Tarek	Ypsilanti	MI		
Shih; Amy	Ann Arbor	MI		
Myc; Andrzej	Ann Arbor	MI		

US-CL-CURRENT: 424/678; 424/600, 424/679, 424/750, 424/769, 424/776, 514/23, 514/561, 514/938

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 11. Document ID: US 6506411 B2

L8: Entry 11 of 35 File: USPT Jan 14, 2003

US-PAT-NO: 6506411
DOCUMENT-IDENTIFIER: US 6506411 B2

TITLE: Anti-angiogenic compositions and methods of use

DATE-ISSUED: January 14, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hunter; William L.	Vancouver			CA
Machan; Lindsay S.	Vancouver			CA
Arsenault; A. Larry	Paris			CA

US-CL-CURRENT: 424/501; 424/502

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw D

☐ 12. Document ID: US 6475517 B1

L8: Entry 12 of 35 File: USPT Nov 5, 2002

US-PAT-NO: 6475517
DOCUMENT-IDENTIFIER: US 6475517 B1

TITLE: Method for preparing closed vesicles

DATE-ISSUED: November 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Tagawa; Toshiaki	Kanagawa			JP
Hosokawa; Saiko	Kanagawa			JP
Nagaike; Kazuhiro	Kanagawa			JP

US-CL-CURRENT: 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw D

☐ 13. Document ID: US 6444660 B1

L8: Entry 13 of 35 File: USPT Sep 3, 2002

US-PAT-NO: 6444660
DOCUMENT-IDENTIFIER: US 6444660 B1

TITLE: Lipid soluble steroid prodrugs

DATE-ISSUED: September 3, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		
Shen; DeKang	Tucson	AZ		

US-CL-CURRENT: 514/180

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw D

☐ 14. Document ID: US 6416740 B1

L8: Entry 14 of 35 File: USPT Jul 9, 2002

US-PAT-NO: 6416740
DOCUMENT-IDENTIFIER: US 6416740 B1

TITLE: Acoustically active drug delivery systems

DATE-ISSUED: July 9, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		

US-CL-CURRENT: 424/9.52; 424/450, 424/9.5, 424/9.51

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 15. Document ID: US 6399590 B2

L8: Entry 15 of 35 File: USPT Jun 4, 2002

US-PAT-NO: 6399590
DOCUMENT-IDENTIFIER: US 6399590 B2

TITLE: Phosphoglycolipid and methods for its use

DATE-ISSUED: June 4, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Elliott; Gary T.	Stevensville	MT		
Weber; Patricia A.	Hamilton	MT		
Sowell; C. Gregory	Hamilton	MT		

US-CL-CURRENT: 514/53; 536/123.13, 536/53, 536/55, 536/55.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 16. Document ID: US 6387396 B2

L8: Entry 16 of 35 File: USPT May 14, 2002

US-PAT-NO: 6387396
DOCUMENT-IDENTIFIER: US 6387396 B2
**** See image for Certificate of Correction ****

TITLE: Compositions containing at least one nucleic acid

DATE-ISSUED: May 14, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY

Mahy; Patrick	Talence	FR
Roux; Didier	Merignac	FR
Laversanne; Rene	Pessac	FR
Amedee; Joelle	Pessac	FR
Freund; OLivier	Bordeaux	FR

US-CL-CURRENT: 424/450; 424/417, 424/420, 424/93.21, 435/458

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 17. Document ID: US 6296870 B1

L8: Entry 17 of 35 File: USPT Oct 2, 2001

US-PAT-NO: 6296870
DOCUMENT-IDENTIFIER: US 6296870 B1

TITLE: Liposomes containing active agents

DATE-ISSUED: October 2, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Needham; David	Durham	NC		
Sarpal; Ranjit S.	Durham	NC		

US-CL-CURRENT: 424/450; 424/1.21, 424/9.321, 424/9.51, 424/94.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 18. Document ID: US 6231834 B1

L8: Entry 18 of 35 File: USPT May 15, 2001

US-PAT-NO: 6231834
DOCUMENT-IDENTIFIER: US 6231834 B1

TITLE: Methods for ultrasound imaging involving the use of a contrast agent and multiple images and processing of same

DATE-ISSUED: May 15, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		
Fritz; Thomas A.	Tucson	AZ		
Gertz; Edward W.	Paradise Valley	AZ		

US-CL-CURRENT: 424/9.51; 424/9.52, 600/431

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 19. Document ID: US 6143321 A

L8: Entry 19 of 35 File: USPT Nov 7, 2000

US-PAT-NO: 6143321
DOCUMENT-IDENTIFIER: US 6143321 A

TITLE: Liposomes containing active agents

DATE-ISSUED: November 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Needham; David	Durham	NC		
Sarpal; Ranjit S.	Durham	NC		

US-CL-CURRENT: 424/450; 424/1.21, 424/9.321, 424/9.51, 424/94.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 20. Document ID: US 6139819 A

L8: Entry 20 of 35 File: USPT Oct 31, 2000

US-PAT-NO: 6139819
DOCUMENT-IDENTIFIER: US 6139819 A
** See image for Certificate of Correction **

TITLE: Targeted contrast agents for diagnostic and therapeutic use

DATE-ISSUED: October 31, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		
Fritz; Thomas A.	Tucson	AZ		
Gertz; Edward W.	Paradise Valley	AZ		

US-CL-CURRENT: 424/9.52; 424/450, 424/9.51

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 21. Document ID: US 6123923 A

L8: Entry 21 of 35 File: USPT Sep 26, 2000

US-PAT-NO: 6123923

DOCUMENT-IDENTIFIER: US 6123923 A
**** See image for Certificate of Correction ****

TITLE: Optoacoustic contrast agents and methods for their use

DATE-ISSUED: September 26, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		
Wu; Yunqiu	Tucson	AZ		

US-CL-CURRENT: 424/9.52; 424/450, 424/9.1, 424/9.2, 424/9.3, 424/9.6, 514/410

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 22. Document ID: US 6090800 A

L8: Entry 22 of 35 File: USPT Jul 18, 2000

US-PAT-NO: 6090800
DOCUMENT-IDENTIFIER: US 6090800 A
**** See image for Certificate of Correction ****

TITLE: Lipid soluble steroid prodrugs

DATE-ISSUED: July 18, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Unger; Evan C.	Tucson	AZ		
Shen; DeKang	Tucson	AZ		

US-CL-CURRENT: 514/180; 552/574

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 23. Document ID: US 6028066 A

L8: Entry 23 of 35 File: USPT Feb 22, 2000

US-PAT-NO: 6028066
DOCUMENT-IDENTIFIER: US 6028066 A

TITLE: Prodrugs comprising fluorinated amphiphiles

DATE-ISSUED: February 22, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY

Unger; Evan C. Tucson AZ

US-CL-CURRENT: 514/180; 514/169, 552/507

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 24. Document ID: US 6013640 A

L8: Entry 24 of 35 File: USPT Jan 11, 2000

US-PAT-NO: 6013640
DOCUMENT-IDENTIFIER: US 6013640 A

TITLE: Phosphoglycolipid and methods for its use

DATE-ISSUED: January 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Elliott; Gary T.	Stevensville	MT		
Weber; Patricia A.	Hamilton	MT		
Sowell; C. Gregory	Hamilton	MT		

US-CL-CURRENT: 514/53; 536/123.13, 536/53, 536/55, 536/55.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 25. Document ID: US 5977044 A

L8: Entry 25 of 35 File: USPT Nov 2, 1999

US-PAT-NO: 5977044
DOCUMENT-IDENTIFIER: US 5977044 A

TITLE: Liquid peracid precursor colloidal dispersions: macroemulsions

DATE-ISSUED: November 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Peterson; David	Pleasanton	CA	94566	
McManus; James D.	Tracy	CA	95376	
Ottoboni; Thomas B.	Belmont	CA	94002	
Ungermann; Charles B.	Livermore	CA	94550	
Van Buskirk; Gregory	Danville	CA	94562	
Zhou; Boli	Antioch	CA	94509	

US-CL-CURRENT: 510/277; 252/186.38, 252/186.41, 510/303, 510/312, 510/417, 516/74, 516/76

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Drawi D

☐ 26. Document ID: US 5954998 A

L8: Entry 26 of 35 File: USPT Sep 21, 1999

US-PAT-NO: 5954998
DOCUMENT-IDENTIFIER: US 5954998 A

TITLE: Liquid peracid precursor colloidal dispersions: oil-core vesicles

DATE-ISSUED: September 21, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zhou; Boli	Antioch	CA		
McManus; James D.	Tracy	CA		
Sudbury; Barry A.	Pleasanton	CA		
Van Buskirk; Gregory	Danville	CA		

US-CL-CURRENT: 252/186.25; 252/186.26, 252/186.38, 252/186.39, 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Drawi D

☐ 27. Document ID: US 5882679 A

L8: Entry 27 of 35 File: USPT Mar 16, 1999

US-PAT-NO: 5882679
DOCUMENT-IDENTIFIER: US 5882679 A

TITLE: Liposomes containing active agents aggregated with lipid surfactants

DATE-ISSUED: March 16, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Needham; David	Durham	NC		

US-CL-CURRENT: 424/450

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Drawi D

☐ 28. Document ID: US 5877137 A

L8: Entry 28 of 35 File: USPT Mar 2, 1999

US-PAT-NO: 5877137
DOCUMENT-IDENTIFIER: US 5877137 A

TITLE: Liquid peracid precursor colloidal dispersions oil-core vesicles

DATE-ISSUED: March 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zhou; Boli	Antioch	CA		
McManus; James D.	Tracy	CA		
Sudbury; Barry A.	Pleasanton	CA		
Buskirk; Gregory Van	Danville	CA		

US-CL-CURRENT: 510/277; 252/186.25, 252/186.26, 252/186.38, 252/186.39, 424/450, 510/312, 510/376, 510/378

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 29. Document ID: US 5877136 A

L8: Entry 29 of 35 File: USPT Mar 2, 1999

US-PAT-NO: 5877136
DOCUMENT-IDENTIFIER: US 5877136 A

TITLE: Liquid peracid precursor colloidal dispersions: Liquid crystals

DATE-ISSUED: March 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Scheuing; David R.	Danville	CA		
McManus; James D.	Tracy	CA		
Van Buskirk; Gregory	Danville	CA		

US-CL-CURRENT: 510/277; 252/186.38, 252/299.01, 510/312, 510/336, 510/417

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 30. Document ID: US 5846951 A

L8: Entry 30 of 35 File: USPT Dec 8, 1998

US-PAT-NO: 5846951
DOCUMENT-IDENTIFIER: US 5846951 A
**** See image for Certificate of Correction ****

TITLE: Pharmaceutical compositions

DATE-ISSUED: December 8, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gregoriadis; Gregory	Middlesex			GB

US-CL-CURRENT: 514/54; 424/450, 424/461, 514/42

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Drawi D

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Terms	Documents
L7 and enzyme	35

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☐	L8	L7 and enzyme	35
☐	L7	L6 and $block	74
☐	L6	surfactant adj3 vesicle	226
☐	L5	surfactant adj5 vesicle	289
☐	L4	pluronic adj10 vesicle	1
☐	L3	pluronic adj5 vesicle	0
☐	L2	L1 and enzyme	73
☐	L1	pluronic same vesicle	105

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L4: Entry 2 of 2 File: USPT May 27, 2003

US-PAT-NO: 6569528
DOCUMENT-IDENTIFIER: US 6569528 B2

TITLE: Amphiphilic biodegradable block copolymers and self-assembled polymer aggregates formed from the same in aqueous milieu

DATE-ISSUED: May 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Nam; Yoon Sung	Kyunggi-do			KR
Kang; Hyung Seok	Kyunggi-do			KR
Han; Sang Hoon	Kyunggi-do			KR
Chang; Ih Seop	Kyunggi-do			KR

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Pacific Corporation	Seoul			KR	03

APPL-NO: 10/ 173728 [PALM]
DATE FILED: June 19, 2002

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
KR	2001-36048	June 23, 2001

INT-CL: [07] B32 B 15/02

US-CL-ISSUED: 428/402; 528/354, 528/361, 525/450, 525/540
US-CL-CURRENT: 428/402; 525/450, 525/540, 528/354, 528/361

FIELD-OF-SEARCH: 528/354, 528/361, 525/450, 525/540, 428/402

PRIOR-ART-DISCLOSED:

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A. V. Kabanov et al., A New Class of Drug Carriers: Micelles of Poly(oxyethylene)-poly(oxypropylene) Block Copolymers as Microcontainers for Drug Targeting from Blood in Brain, Journal of Controlled Release, 22, 141.about.158, 1992.
C. Allen et al., Polycaprolactone--b-poly(ethylene oxide) Copolymer Micelles as a Delivery Vehicle for Dihydrotestosterone, Journal of Controlled Release, 63, 275.about.286, 2000.
T. Inoue et al., An AB Block Copolymer of Oligo(methyl methacrylate) and Poly (acrylic acid) for Micellar Delivery of Hydrophobic Drugs, Journal of Controlled

Release, 51, 221.about.2229, 1998.
A. Harada et al., Formation of Polyion Complex Micelles in an Aqueous Milieu from a Pair of Oppositely-Charged Block Copolyers with Poly(ethylene glycol) Segments, Macromolecules, 28, 5294.about.5299, 1995.
A. Harada et al., Novel Polyion Complex Micelles Entrapping Enzyme Molecules in the Core: Preparation of Narrowly-Distributed Micelles from Lysozyme and Poly(ethylene glycol)--Poly(aspartic acid) Block Copolymer in Aqueous Medium, Macromolecules, 31, 288.about.294, 1998.
K. Yu et al., Multiple Morphologies in Aqueous Solutions of Aggregates of Polystyrene-block-poly(ethylene oxide) Diblock Copolymers, Macromolecules, 29, 6359.about.6361, 1996.
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L. Zhang et al., Multiple Morphologies of "Crew-Cut" Aggregates of Polystyrene-b-poly(acrylic acid) Block Copolymers, Science, 268, 1728.about.1731, 1995.
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ART-UNIT: 1711

PRIMARY-EXAMINER: Acquah; Samuel A.

ABSTRACT:

There are provided amphiphilic biodegradable block copolymers comprising polyethylenimine (PEI) as a hydrophilic block and aliphatic polyesters as a hydrophobic block, which can form various size of polymer aggregates and have very low critical micelle concentration, approximately 10.sup.-3 g/l in comparison with low-molecular-weight micelle, and self-assembled polymer aggregates formed from the block copolymers in aqueous milieu, which can be applied to solubilization of insoluble drug and a delivery system of proteins, genes or drugs.

19 Claims, 9 Drawing figures

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L8: Entry 1 of 19 File: USPT Apr 6, 2004

US-PAT-NO: 6716450
DOCUMENT-IDENTIFIER: US 6716450 B1

TITLE: Enhancing protein activity through nanoencapsulation

DATE-ISSUED: April 6, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yin; Ray	Newark	DE		
Cheng; Tu-Chen	Timonium	MD		
Durst; H. Dupont	Bel Air	MD		
Qin; Dujie	Bel Air	MD		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The United States of America as represented by the Secretary of the Army	Washington	DC			06

APPL-NO: 09/ 859260 [PALM]
DATE FILED: May 17, 2001

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATIONS This application is a non-provisional continuation of provisional application Serial No. 60/205,034 filed on May 18, 2000.

INT-CL: [07] A61 K 9/48, A61 K 31/74, A61 K 31/765

US-CL-ISSUED: 424/451; 424/78.18, 424/78.19, 424/489
US-CL-CURRENT: 424/451; 424/489, 424/78.18, 424/78.19

FIELD-OF-SEARCH: 424/451, 424/78.18, 424/78.19, 424/489

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

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	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5714166	February 1998	Tomalia et al.	
☐	5919442	July 1999	Yin et al.	424/78.18

ART-UNIT: 1615

PRIMARY-EXAMINER: Page; Thurman K.

ASSISTANT-EXAMINER: Fubara; Blessing

ATTY-AGENT-FIRM: Biffoni; Ulysses John

ABSTRACT:

Nanocapsules useful for encapsulating bioactive molecules such as proteins are disclosed. These nanocapsules are comprised of branched or hyperbranched polymers and copolymers and have a core-shell structure forming a pocket volume appropriate for complexing and retaining enzymes and other bioactive molecules. The nanoencapsulated bioactive molecule is stable in extreme temperatures and pH, soluble in aqueous or organic solvents, and can be lyophilized to a dry powder for long-term storage without loss of enzyme activity.

24 Claims, 13 Drawing figures

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